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The therapeutic effect of an organosulfur-derived capsule (Nicovid) as a supplementary treatment for covid-19 patients

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ABSTRACT

Background: From the emergence of the novel corona virus, several drugs have been proposed for its treatment. New compounds are being tested on a regular basis to find the most effective drug for ameliorating the symptoms of this infection. Organosulfur-rich compounds extracted from *Allium sativum* (garlic) has been found to have anti-viral and therapeutic effects in the management of COVID-19. Thus, this study has been designed to evaluate the efficacy of an organosulfur-derived capsule in the management of COVID-19 patients. *Material and Methods*: 756 patients with COVID-19 infection were enrolled for this randomized case-control study in a hospital in northern Iran, which were randomly divided into placebo and organosulfur group. From 22 September 2020 to 19 March 2021, the organosulfur group was given an organosulfur-derived capsule (90 mg/kg) three times a day (every eight hours) for 14 days. Placebo capsules were given to the placebo group on the same regiment. 720 patients completed the treatment (n=360 in each group). Clinical symptoms, vital signs, and laboratory tests were evaluated both before and after the treatment. *Result*: A significant difference was found in the prevalence of cough (p-value=0.015), dyspnoea (p-value=0.014), and myalgia (p-value=0.001) along with O2-saturation (p-value=0.023), platelet (p-value=0.023) and CRP (p-value<0.001) levels between placebo and organosulfur groups. Other symptoms haven't shown a statistically significant difference. *Conclusion*: The present study showed that supplementary treatment of COVID-19 patients with organosulfur compounds can remarkably improve the clinical symptoms and O2-saturation along with platelet and CRP levels.

Keywords: COVID-19, SARS-COV-2, *Allium sativum*, Organosulfur, Nicovid, Supplementary treatment.

1. INTRODUCTION

In late December of 2019 in Wuhan, China there has been a report of a novel virus and ever since the world is in struggle with (Huang et al., 2020). The World Health Organisation officially called it COVID-19 and the International Committee on Taxonomy of Viruses (ICTV) named it SARS-COV-2 (severe acute respiratory syndrome coronavirus 2) (Wang et al., 2020). This novel virus is a member of the β-coronavirus family. In comparison with Severe Acute Respiratory Syndrome (SARS-COV) and Middle East Respiratory Syndrome Coronaviruses (MERS-COV), COVID-19 has high infectivity and transmissibility while lower mortality rate (Liu et al., 2020b). More than 167 million cases of this novel virus have been reported, among which more than three million have died until now (Worldometer, 2021). The novel virus has vast variety of symptoms such as cough, fever, fatigue, body aches, and shortness of breath. Some uncommon symptoms include headache, nasal congestion, loss of taste or smell, pain in muscles or joints, chills, nausea, and diarrhoea (Grant et al., 2020, Huang et al., 2020). Since the outbreak, managing the patients has been of utmost importance for healthcare systems globally. Despite the fact that severe lung injury has been described at all ages, among the high-risk individuals, such as the elder people and those who suffer from multi-morbidities, the COVID-19 is more likely to cause acute respiratory distress syndrome (ARDS) and multiorgan failure, which subsequently causes severe acute respiratory failure and high death rates (Pascarella et al., 2020; Lake, 2020; Liu et al., 2020a). Several drugs have been proposed for treating COVID-19 such as chloroquine and hydroxychloroquine, darunavir, oseltamivir, remdesivir, etc (Tarighi et al., 2021). Recent studies have investigated the effect of *Allium sativum* (garlic) on the treatment of viral infections. Organosulfur-rich compounds extracted from garlic has been suggested to have therapeutic effects in the management of COVID-19 (Donma and Donma, 2020; Khubber et al., 2020). However, few studies have assessed this important capacity with limited number of subjects. Hence, the aim of this research was the effect of an organosulfur-derived capsule in the management of COVID-19 patients.

2. MATERIAL AND METHODS

Study Design

This was a randomized case-control study on 756 patients who were previously diagnosed with COVID-19 infection, based on clinical examination of an emergency medicine specialist, an infectious disease specialist, and final affirmation by RT-PCR test, in a hospital in northern Iran. The inclusion and exclusion criteria are summarised in Table 1.

Table 1 Summary of Inclusion and Exclusion Criteria

Inclusion	Exclusion
positive RT-PCR result	history of allergies to organosulfur compounds (such as garlic or onion)
	history of hypotension
age between 18 to 70	history of GI bleeding
	hypotension at the beginning of study
absence of pregnancy	immunodeficiency
	chemotherapy
absence of lactation	bone marrow transplant
	autoimmune patients
	need of ventilation

In our study, 756 patients were randomly divided into control group and organosulfur group during 22 September 2020 to 19 March 2021, the latter was given organosulfur-derived capsules (90 mg/kg) and placebo to the former group. Among these 756 patients, 720 patients completed the treatment (n=360 in each group). The capsules were given to each group three times a day (every eight hours) for 14 days. The main composition of the organosulfur-derived capsule was allicin (L-cysteine) which was oxidatively stable by allotropic process and an active ingredient. The appearance of an organosulfur-derived capsule and the placebo capsule was similar in order to blind the results. The capsules were given to the patients either by their nurse or their physician. Also, both groups received routine treatment of SARS-COV-2 infection based on the latest national guidelines.

Clinical symptoms (cough, myalgia, anosmia, chill, consciousness, diarrhoea, headache, nasal congestion, nausea and vomiting, sore throat, weakness, and taste disorder) along with vital signs (respiratory rate, pulse rate, temperature, and O2-saturation) and

laboratory tests (white blood cells, lymphocyte, platelet, red blood cells, haemoglobin, and C-reactive protein) were evaluated both before and after the treatment. This article was approved by the hospital ethics committee with code IR.NTB.1399.091.

Statistical Analysis

Descriptive statistics was used in terms of frequency (%) or mean±SD to describe the data. The McNemar's test and Wilcoxon Signed Rank Sum test were used for pre- and post-treatment analyses within each group. Chi-Square test and Mann-Whitney U test were used to compare the placebo group with the organosulfur group. The data was gathered and analyzed via STATA 14.0 and p-values under 0.05 were considered as statistically significant.

3. RESULTS

There were 360 patients in placebo group, among which 153 (42.50%) and 207 (57.05%) were female and male, respectively. Also, among the 360 patients in organosulfur group, 162 (45%) patients were female and 198 (55%) were male. The mean age (±SD) was 48.55±10.07 years among the placebo group and 48.37±9.89 years among the organosulfur group. Based on chi-squared test and t-test, no significance difference was observed between these variables. The demographic information shows in Table 2.

Table 2 Summary of Demographic Characteristics

		Placebo group	Organosulfur group	p-value
Sex	Female	153 (42.50%)	162 (45%)	0.499[1]
	Male	207 (57.05%)	198 (55%)	
Age	mean±SD	48.55±10.07	48.37±9.89	0.817[2]
[1] Chi-Square test [2] Independent T-test				

Table 3 Prevalence of Symptoms and the Comparison between the Organosulfur and Placebo Groups

	Pre-treatment			Post-treatment				
Variables	Placebo (%)	Organosulfur (%)	p-value[1]	Placebo (%)	Organosulfur (%)	p-value[2]	p-value[3]	p-value[4]
Cough	74.44	77.78	0.294	34.17	25.83	0.015*	P<0.05	P<0.05
Dyspnoea	76.11	73.61	0.439	55.28	46.11	0.014*	P<0.05	P<0.05
Myalgia	68.06	65.28	0.429	25.83	15.83	0.001*	P<0.05	P<0.05
Anosmia	21.11	25	0.215	11.11	8.06	0.164	P<0.05	P<0.05
Chill	45.68	48.89	0.389	3.06	1.67	0.220	P<0.05	P<0.05
Consciousness	94.17	92.20	0.296	98.61	99.17	0.477	P<0.05	P<0.05
Diarrhea	4.17	4.44	0.854	1.39	1.67	0.761	P<0.05	P<0.05
Headache	34.72	39.17	0.217	25.83	22.22	0.257	P<0.05	P<0.05
Nausea and Vomiting	21.17	25.56	0.165	2.78	5.56	0.062	P<0.05	P<0.05
Sore Throat	10.86	9.17	0.449	3.06	4.44	0.327	P<0.05	P<0.05
Weakness	67.22	61.11	0.087	53.61	48.89	0.205	P<0.05	P<0.05
Taste Disorder	24.44	20.56	0.211	6.67	3.61	0.063	P<0.05	P<0.05
1. comparison between organosulfur and placebo groups in pre-treatment (Chi-square and Mann-Whitney U test) 2. comparison between organosulfur and placebo groups in post-treatment (Chi-square and Mann-Whitney U test) 3. comparison between data of pre- and post-treatment in placebo group (McNemar's test and Wilcoxon Signed rank test) 4. comparison between data of pre- and post-treatment in organosulfur group (McNemar's test and Wilcoxon Signed rank test)								

The most common symptoms among the placebo group were dyspnoea (76.11%), cough (74.44%), myalgia (68.06%), weakness (67.22%), chill (45.68%), and headache (34.72%) among the pre-treatment placebo group and cough (77.78%), dyspnoea (73.61%), myalgia (65.28%), weakness (61.11%), chill (58.89%), and headache (39.17%) among the pre-treatment organosulfur group. Also, diarrhoea was the most uncommon symptom in pre-treatment groups, 4.17% and 4.44% for placebo and organosulfur groups, respectively. According to chi-squared test, no significant differences were observed among the pre-treatment placebo or organosulfur groups. Further information regarding the prevalence of different symptoms in pre-treatment groups is summarised in Table 3 and Figure 1.

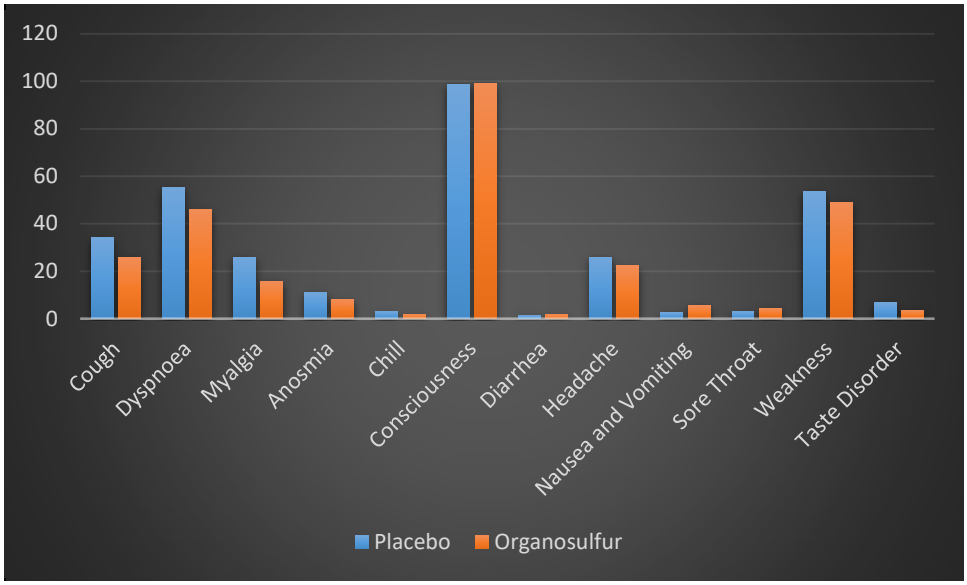

Figure 1 Comparison of symptoms between the organosulfur and placebo groups in post-treatment

In post-treatment groups, the most common symptoms were weakness (53.61%), dyspnoea (55.28%), cough (34.17%), myalgia (25.83%), and headache (25.83%) among the placebo group and weakness (48.89%), cough (25.83%), dyspnoea (46.11%), myalgia (15.83%), and headache (22.22%) among the organosulfur group. Between the placebo and organosulfur groups in the prevalence of cough (p-value=0.015), dyspnoea (p-value=0.014), and myalgia (p-value=0.001) there was a significant difference. Among other symptoms between placebo and organosulfur groups, no significant difference was found. The comparison between pre- and post-treatment placebo and organosulfur group, based on McNemar's test and Wilcoxon Signed Rank Sum test, showed statistically significant difference between all of the symptoms. Further information regarding the prevalence of different symptoms in post-treatment groups is summarised in Table 3. In pre-treatment group, the mean±SD respiratory rate, temperature, and O2-saturation were 19.66±0.46, 96.18±3.62, and 90.4±3.56 for placebo groups, respectively. Also, among the organosulfur group, the mean±SD respiratory rate, temperature, and O2-saturation were 19.65±0.34, 38.2±0.69, and 90.8±3.31, respectively. Regarding the vital signs between placebo and organosulfur groups no significant difference was found.

In post treatment group, the mean±SD respiratory rate, temperature, and O2-saturation were 22.16±3.65, 36.77±0.31, and 94.84±3.14 for placebo groups, and 22.7±3.67, 36.79±0.27, 95.29±3.16 for organosulfur group, respectively. Importantly, there was a statistically significant difference, among the placebo and organosulfur groups regarding the O2-saturation level (p-value=0.023). Also, in each of the placebo and organosulfur groups, there was a significant difference between respiratory rate, pulse rate, temperature, and O2-saturation in pre- and post-treatment groups. Also, further information regarding the summary of vital signs in pre- and post-treatment groups is available in Table 4.

Regarding the laboratory tests, the mean±SD platelet and C-reactive protein (CRP) levels were 365±34.57 and 31±6.91 for pre-treatment placebo group and 360±34.56 and 31.91±6.78 for pre-treatment organosulfur group. Also, the mean±SD platelet and CRP levels for post-treatment group were 352.91±19.56 and 2.11±1.02 for placebo groups and 347.5±17.28 and 1.79±0.94 for organosulfur groups. There was a significant difference between the platelet (p-value=0.023) and CRP (p-value<0.001) levels of placebo and organosulfur groups in post-treatment patients. Also, further information regarding the summary of laboratory tests in pre- and post-treatment groups is available in Table 5.

Table 4 Summary of vital signs examination and the comparison between the organosulfur and placebo groups.

	Pre-treatment			Post-treatment				
Variables	Placebo (mean±SD)	Organosulfur (mean±SD)	p-value[1]	Placebo (mean±SD)	Organosulfur (mean±SD)	p-value[2]	p-value[3]	p-value[4]
Respiratory rate	19.66±0.46	19.65±0.34	0.145	22.16±3.65	22.7±3.67	0.052	P<0.05	P<0.05
Pulse rate	96.18±3.62	95.44±2.7	0.337	84.16±6.61	84±6.91	0.748	P<0.05	P<0.05
Temperature	38.11±0.71	38.2±0.69	0.106	36.77±0.31	36.79±0.27	0.331	P<0.05	P<0.05
O2saturation	90.4±3.56	90.8±3.31	0.065	94.84±3.14	95.29±3.16	0.023*	P<0.05	P<0.05

1. comparison between organosulfur and placebo groups in pre-treatment (Chi-square and Mann-Whitney U test)
2. comparison between organosulfur and placebo groups in post-treatment (Chi-square and Mann-Whitney U test)
3. comparison between data of pre- and post-treatment in placebo group (McNemar's test and Wilcoxon Signed rank test)
4. comparison between data of pre- and post-treatment in organosulfur group (McNemar's test and Wilcoxon Signed rank test)

Table 5 Summary of Laboratory Tests the Comparison Between the Organosulfur and Placebo Groups.

	Pre-treatment			Post-treatment				
Variables	Placebo (mean±SD)	Organosulfur (mean±SD)	p-value[1]	Placebo (mean±SD)	Organosulfur (mean±SD)	p-value[2]	p-value[3]	p-value[4]
White blood cell	12.5±0.34	12.45±0.39	0.051	7.70±0.69	7.89±0.69	0.052	P<0.05	P<0.05
Lymphocyte	26.2±1.38	26±1.38	0.052	23.1±0.69	23.28±0.70	0.053	P<0.05	P<0.05
Platelet	365±34.57	360±34.56	0.052	352.91±19.56	347.5±17.28	0.023*	P<0.05	P<0.05
Red blood cell	4.82±0.07	4.82±0.06	0.106	4.89±0.07	4.90±0.07	0.106	NS	NS
Haemoglobin	13.6±0.96	13.55±1.01	0.332	13.50±0.42	13.62±0.40	0.052	NS	NS
CRP	31±6.91	31.91±6.78	0.075	2.11±1.02	1.79±0.94	<0.001*	P<0.05	P<0.05

1. comparison between organosulfur and placebo groups in pre-treatment (Chi-square and Mann-Whitney U test)
2. comparison between organosulfur and placebo groups in post-treatment (Chi-square and Mann-Whitney U test)
3. comparison between data of pre- and post-treatment in placebo group (McNemar's test and Wilcoxon Signed rank test)
4. comparison between data of pre- and post-treatment in organosulfur group (McNemar's test and Wilcoxon Signed rank test)

4. DISCUSSION

The bioactive compounds in *Allium sativum* (garlic) has been found to have virucidal effects (Weber et al., 1992). Various studies have reported that organosulfur compounds in *Allium sativum* have antiviral activities against viral and specifically respiratory infections through inhibiting the entrance of the virus into host cells, blocking viral RNA polymerase, reverse transcriptase, and DNA synthesis. It also prevents widespread viral infections through enhancing the immune system and has prophylactic effects against such infections (Rouf et al., 2020; Choi, 2018). Other potential health benefits of garlic include; antioxidant capacity, anti-inflammatory properties, stimulatory immunomodulatory effects, hypertensive properties, anti-hemagglutination and therapeutic effects against cancer, cardiovascular diseases, metabolic syndrome, and diabetes (Petropoulos et al., 2018; Serrano et al., 2018; Tattelman, 2005; Kim and Kwon, 2009; Zuniga et al., 2019; Zhu et al., 2018; Choudhary et al., 2018; Sujithra et al., 2019; Ried, 2016; Chavan et al., 2016).

The present study showed that supplementary treatment of COVID-19 patients with organosulfur compounds can significantly improve clinical symptoms, O2-saturation along with blood parameters such as platelet and CRP levels. Cerebrovascular accidents such as stroke due to cerebral thrombosis and/or thromboembolism occurs among severely infected people with COVID-19 (Nannoni et al., 2021). The decreased platelet level in post-treatment organosulfur group could be suggestive of the potential therapeutic effect of these compounds in preventing cerebrovascular accidents. By upregulating the detoxifying enzymes and

increasing cellular glutathione level in vascular endothelial cells, organosulfur compounds can prevent reactive oxygen damage under hypoxia, which is a common problem in COVID-19 infection (Horev-Azaria et al., 2009).

A common consequence of COVID-19 infection is the acute lung injury due to inflammatory burst and abrupt allows leaving of pro-inflammatory mediators that persuade the accumulation of intra-alveolar fibrin, which subsequently causes reduced gas exchange (Gallelli et al., 2020). The organosulfur compounds can potentially fasten and improve the repairment of alveolar tissue due to their anti-inflammatory properties and regenerative capacity (Arreola et al., 2015; Shen et al., 2019; Zhang et al., 2008). An in vivo study suggests that these compounds may even protect against hypoxic pulmonary vasoconstriction (Kim-Park and Ku, 2000).

Various studies have confirmed the antiviral activity of organosulfur compounds against certain family of viruses, such as Coronavirus (CoV) (Mehrbod et al., 2013). Several studies have suggested the potential of organosulfur compounds in supplementary treatment of COVID-19 infected patients (Thuy et al., 2020; Oso et al., 2020). One study suggests that adjuvant therapy with these compounds may improve the toxicity of the main therapeutic drugs (Khubber et al., 2020). Another study addresses the preventive effect of these compounds against COVID-19 infection through boosting immune system and repression of proinflammatory cytokines (Donma and Donma, 2020). Overall, the supplementary treatment of organosulfur-derived compounds along with routine antiviral and other drug therapies is an effective strategy to lessen the severity of COVID-19 infection in patients with one or several comorbidities. Our study showed the significant clinical efficacy of an organosulfur-derived capsule among COVID-19 infected patients. Further studies and trials can elucidate the concise chemical and physiological patterns of these compounds.

5. CONCLUSIONS

In conclusion, the present study showed that an organosulfur-derived capsule can significantly improve clinical symptoms (such as coughing, dyspnoea, and myalgia), vital signs (O2-saturation), and blood parameters (such as platelet and CRP) among COVID-19 patients. The supplementary treatment of these patients with organosulfur compounds is effective to lessen the severity of the infection.

Consent for publication

All authors declare that they have consented for publication

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the design of the study, as well as data collection and analysis, and the writing of the manuscript. All authors read and approved the final manuscript.

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Not applicable.

Conflict of Interest

There is no contradiction in the article.

Ethical approval

The study was approved by the Medical Ethics Committee of Our Hospital. (Ethical approval code: IR.NTB.1399.091).

Data and materials availability

All data associated with this study are present in the paper.

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